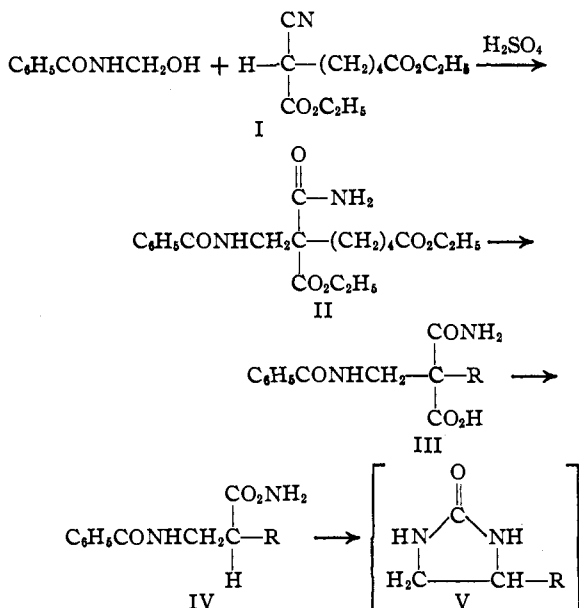


following series of reactions.



Since a supply of ethyl δ -bromovalerate was available, from which diethyl α -cyanopimelate (I) was readily prepared, the synthesis of the next lower homolog (V, R = (CH₂)₄COOH)¹ was attempted. In practice, the conversion of IV (R = (CH₂)₄COOH) into V (R = (CH₂)₄COOH) was not achieved by the method of Kanewskaja² for the conversion of β -benzoylamino-propionamide (IV; R = H) into ethyleneurea (V, R = H). An interesting and efficient synthesis of the penultimate compound IV (R = (CH₂)₄COOH) was, however, accomplished.

This synthesis was based on the condensation of N-hydroxymethylbenzamide with diethyl α -cyanopimelate in the presence of concentrated sulfuric acid. Previous instances of the reaction of N-hydroxymethylbenzamide with compounds containing active methylene groups have been reported by Monti.³

Experimental^{4,5}

Diethyl α -Cyanopimelate (I).—To a solution of 4.25 g. (0.185 atom) of sodium in 230 cc. of absolute alcohol was added 21.4 g. (0.189 mole) of ethyl cyanoacetate (Eastman Kodak Co.) and 39 g. (0.186 mole) of ethyl δ -bromovalerate.⁶ After refluxing for three and one-half hours the neutral mixture was concentrated to about one-half its original volume. Water was added and the oily layer which separated was taken up in ether. After washing and drying, the ether was distilled from this solution and the residue was distilled under reduced pressure. The fraction (19.7 g.) boiling from 160 to 200° at 3 mm. was collected. Redistillation gave 16.7 g. (37% yield) of a colorless liquid, b. p. 161–165° (3 mm.).

(2) Kanewskaja, *Ber.*, **69**, 266 (1936).

(3) Monti, *Gazz. chim. ital.*, **60**, 39 (1930); *C. A.*, **24**, 4013 (1930).

(4) All melting points are corrected.

(5) The microanalyses were performed in these Laboratories under the direction of Dr. J. A. Kuck, to whom we are indebted.

(6) Merchant, Wickert and Marvel, *THIS JOURNAL*, **49**, 1828 (1927).

Anal. Calcd. for C₁₂H₁₉NO₄: N, 5.8. Found: N, 5.9, 6.1.

Diethyl α -Benzoylaminoethyl- α -carbamylpimelate (II).—To a mixture of 10 cc. of cold concentrated sulfuric acid and 2.4 g. (0.01 mole) of diethyl α -cyanopimelate, cooled in ice, was added 1.58 g. of N-hydroxymethylbenzamide.⁷ The solution was allowed to stand at 5° for fifteen hours and was then poured onto ice. Crystallization of the precipitate from aqueous alcohol gave small white needles; 3.07 g. (91% yield), m. p. 99–102°. This melting point was raised to 103–105° by several further crystallizations.

Anal. Calcd. for C₂₀H₂₃N₂O₈: C, 61.2; H, 7.2; N, 7.1. Found: C, 61.8, 61.6; H, 7.4, 7.4; N, 7.3, 7.3.

α -Benzoylaminoethyl- α -carbamylpimelic Acid (III, R = (CH₂)₄COOH).—Two grams of II was dissolved in 50 cc. of a solution prepared by shaking absolute alcohol with excess sodium hydroxide pellets for fifteen minutes. A white solid began to precipitate after about ten minutes at room temperature. After standing for fifteen hours water was added and the resulting solution was acidified in the cold. The product precipitated on standing in the cold; 1.44 g. (84% yield), m. p. 176°, dec. Crystallization from water gave fine white needles, m. p. 177°, dec.

Anal. Calcd. for C₁₆H₂₀N₂O₈: C, 57.1; H, 6.0; N, 8.3; neut. equiv., 168. Found: C, 56.9; H, 5.8; N, 8.3; neut. equiv., 170.

7-Benzoylamino-6-carbamylheptylic Acid (IV, R = (CH₂)₄COOH).—Decarboxylation of 7.11 g. of II began at a bath temperature of 175° and proceeded smoothly while the temperature was held at 175–182°. Approximately one mole of gas was collected. The cooled residue was dissolved in dilute sodium hydroxide and the solution was acidified to precipitate the product. Crystallization from aqueous alcohol gave 4.48 g. (73% yield) of fine white needles. This product did not have a definite melting point after several crystallizations, appearing to melt at 145.5–147°, to resolidify partially and to melt completely at 155–156°.

Anal. Calcd. for C₁₅H₂₀N₂O₄: C, 61.6; H, 6.9; N, 9.6; neut. equiv., 292. Found: C, 61.5, 61.7; H, 7.2, 6.9; N, 9.8, 9.6; neut. equiv., 294.

When 7-benzoylamino-6-carbamylheptylic acid reacted with one or two moles of bromine in potassium hydroxide solution,² the starting product was recovered. Treatment with larger quantities of bromine and the use of barium hydroxide or of methanolic alkali also failed to effect the reaction.

(7) Einhorn, Bischkopff and Szelinski, *Ann.*, **348**, 207 (1905).

STAMFORD RESEARCH LABORATORIES
AMERICAN CYANAMID COMPANY

STAMFORD, CONN. RECEIVED SEPTEMBER 12, 1945

An Improved Synthesis of γ -(3,4-Ureylencyclohexyl)-butyric Acid

BY J. P. ENGLISH, R. C. CLAPP, Q. P. COLE AND
J. KRAPCHO

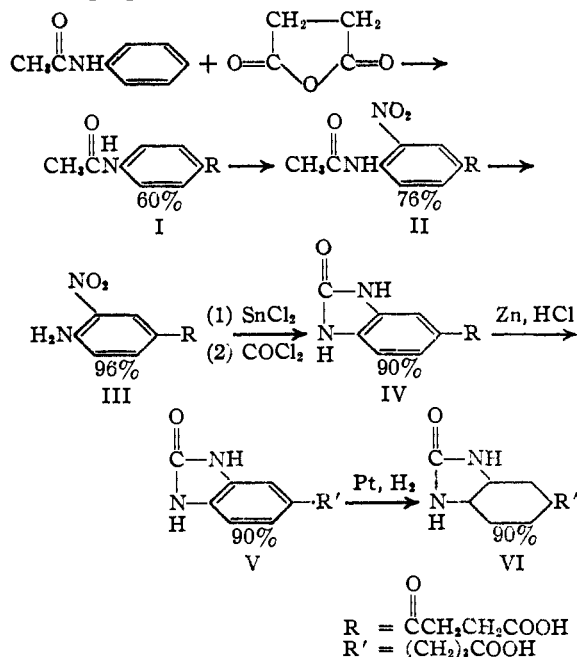
γ -(3,4-Ureylencyclohexyl)-butyric acid (VI) had been previously synthesized¹ in the course of work on the preparation of compounds which would inhibit the utilization of biotin by microorganisms. Further quantities of this compound were desired, and the low yield in the first step of the earlier process led to the development of the present method.

The principal new features of this synthesis are contained in the steps leading to the preparation

(1) English, Clapp, Cole, Halverstadt, Lampen and Roblin, *THIS JOURNAL*, **67**, 295 (1945).

of β -(3,4-ureylenebenzoyl)-propionic acid (IV) since the remaining portion of the preparation is identical with that reported before. The larger quantities used in the present method have led to some modifications in the conditions previously used in the subsequent steps and it has been thought useful to include a description of these improvements as well.

The preparation is outlined in the chart.



The compounds prepared in this way were identical with those prepared earlier, starting with phenyleneurea.¹

The reaction between acetanilide and succinic anhydride has not been reported previously and the relatively good yield obtained in the Friedel-Crafts reaction was somewhat unexpected in view of the paucity of information in the literature on the reaction of anhydrides with anilides.²

An unsuccessful attempt was made to prepare compound III by the ammonolysis of β -(4-methoxy-3-nitrobenzoyl)-propionic acid. This acid was obtained both by the reaction of succinic anhydride with *o*-nitroanisole and by the nitration of β -(4-methoxybenzoyl)-propionic acid.

Experimental

β -(4-Acetylamino-3-nitrobenzoyl)-propionic Acid (I).—A suspension of 185 g. (1.39 mole) of aluminum chloride in 200 cc. of carbon disulfide (previously shaken with mercury) was prepared by grinding the granular product with the solvent in a mortar. The suspension was placed in a flask fitted with a Hershberg stirrer and a condenser and immersed in an ice-bath. Fifty grams (0.37 mole) of acetanilide and 37 g. (0.37 mole) of succinic anhydride were ground together and the mixture was added rapidly to the aluminum chloride suspension with stirring. After the initial reaction had subsided, the cooling bath was removed and stirring was continued until the stiffness of the dark

red mixture halted the stirrer (about two hours). After standing for two days at room temperature the mixture was decomposed with ice. The product was filtered off and washed well with water. The solid was dissolved in aqueous sodium bicarbonate and the solution was filtered. Acidification of the filtrate precipitated a yellow powder, m. p. 193–198°. The yields in several runs were 50–60% of the theoretical. Two crystallizations from alcohol with Norit treatment gave white crystals, m. p. 202–205°. *Anal.* Calcd. for $\text{C}_{12}\text{H}_{11}\text{NO}_4$: C, 61.3; H, 5.6; N, 6.0. Found: C, 61.6, 61.6; H, 5.6, 5.7; N, 6.3, 6.2.

β -(4-Aminobenzoyl)-propionic Acid.—When 2 g. of I was refluxed with 10 cc. of 18% hydrochloric acid for thirty minutes and the resulting solution was cooled a precipitate of the hydrochloride of the amine was obtained. The yield was 1.85 g., m. p. above 300°. The free base was obtained in quantitative yield by acidifying an alkaline solution of this hydrochloride with acetic acid. The amine was obtained as yellow needles after crystallization from water, m. p. 189–190°. The melt was dark green. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_3$: N, 7.3. Found: N, 7.4, 7.5.

β -(4-Acetylamino-3-nitrobenzoyl)-propionic Acid (II).—Fifty grams of I was added with stirring to 150 cc. of ice-cooled fuming nitric acid in seven minutes. Stirring was continued for another eight minutes and the reaction mixture was poured into 1200 cc. of ice and water. The yellow precipitate was filtered off. The yield was 80%; m. p. 151–154°. *Anal.* Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_6$: C, 51.4; H, 4.3; N, 10.0. Found: C, 51.3, 51.4; H, 4.5, 4.5; N, 10.2, 10.3.

β -(4-Amino-3-nitrobenzoyl)-propionic Acid (III).—Eighty grams of II was suspended in 800 cc. of boiling water and 400 cc. of concentrated hydrochloric acid was added. The solid all dissolved and a precipitate then appeared. The yield, 96%, had a m. p. 200–203°; after purification through bicarbonate solution and crystallization from alcohol, m. p. 202–205°. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_5$: C, 50.4; H, 4.2; N, 11.8. Found: C, 50.7, 50.6; H, 4.4, 4.5; N, 11.8, 11.8.

β -(3,4-Ureylenebenzoyl)-propionic Acid (IV).—To a solution of 250 g. of stannous chloride dihydrate in 500 cc. of concentrated hydrochloric acid was added 51 g. of recrystallized III in fifteen minutes. Unless the reaction is kept at 25–30° by occasional cooling a dark product is obtained. The resulting light yellow solution was cooled in an ice-bath and phosgene was bubbled through for one hour, although precipitation appeared to be complete in half this time. The mixture was diluted with 800 cc. of water and it was thoroughly cooled and filtered. The product was treated with Norit in bicarbonate solution and acidification of the clarified filtrate gave 47.3 g. (94%) of a colorless solid, m. p. 298°, dec. This melting point was not depressed by mixture with β -(3,4-ureylenebenzoyl)-propionic acid prepared previously.¹

γ -(3,4-Ureylenephenyl)-butyric Acid (V). The insolubility of IV in hydrochloric acid required the use of such large volumes that a mixture of acetic and hydrochloric acids³ was used as solvent in the larger-sized Clemmensen reductions. To 374 g. of amalgamated zinc were added 200 cc. of glacial acetic acid and 37.4 g. of IV (m. p. 298°). This mixture was heated and 200 cc. of concentrated hydrochloric acid was added. This technique reduced foaming to a minimum. The reaction mixture was refluxed for six hours, 40 cc. of concentrated hydrochloric acid being added after two hours and again after four hours. The resulting solution was decanted from the unreacted zinc into about 3 liters of water and the precipitated product was worked up by the directions of the earlier publication.¹ After treatment with Norit in bicarbonate solution there was obtained 31.5 g. (90%) of colorless product, m. p. 244–249°. Crystallization from aqueous alcohol gave 25.4 g., m. p. 250–252°.

γ -(3,4-Ureylenebenzoyl)-butyric Acid (VI).—Although large quantities of catalyst were required in the

(2) C. A. Thomas, "The Reactions of Aluminum Chloride," Reinhold Publishing Corp., New York, N. Y., 1941, pp. 537, 538.

(3) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 164.

hydrogenation in accordance with previous experience,¹ it was found that the catalyst could be reused and that 18–19 g. could consistently be hydrogenated with 5 g. of catalyst. When a mixture of 10 g. of V, 5 g. of platinum oxide catalyst (J. T. Baker), and 175 cc. of glacial acetic acid was hydrogenated in a Parr apparatus at 30–40 lb., the theoretical quantity of hydrogen was absorbed in three and one-half hours. The catalyst was filtered off and returned to the hydrogenator with 9 g. of V and 175 cc. of acetic acid. After eighteen hours the theoretical quantity of hydrogen had been taken up. The combined acetic acid solutions were worked up as previously described.¹ Crystallization from water gave 17.5 g. (90%) of white solid, m. p. 138–142°.

β -(4-Methoxy-3-nitrobenzoyl)-propionic Acid.—Twenty-five grams of β -(4-methoxybenzoyl)-propionic acid⁴ was nitrated with 50 cc. of fuming nitric acid by the procedure used in the preparation of II. Twenty-six grams (85%) of yellow product, m. p. 126–136°, was obtained. After purification through bicarbonate solution with charcoal, crystallization from methanol gave light yellow needles, m. p. 158–159° (softening at 151°).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 52.2; H, 4.4; N, 5.5. Found: C, 52.4, 52.3; H, 4.4, 4.5; N, 5.5, 5.6.

The same compound was obtained in low yield from *o*-nitroanisole and succinic anhydride with aluminum chloride in nitrobenzene. This same reaction has been carried out with acetyl chloride by Borsche and Barthenheier.⁵

(4) Fieser and Hershberg, *THIS JOURNAL*, **58**, 2314 (1936).

(5) Borsche and Barthenheier, *Ann.*, **553**, 250 (1942).

CHEMOTHERAPY DIVISION

STAMFORD RESEARCH LABORATORIES

AMERICAN CYANAMID COMPANY

STAMFORD, CONN.

RECEIVED SEPTEMBER 19, 1945

1,1-Di-(*p*-chlorophenyl)-ethane

BY OLIVER GRUMMITT, ALLEN C. BUCK AND ERNEST I. BECKER

Need for a small quantity of pure 1,1-di-(*p*-chlorophenyl)-ethane showed that the only preparation reported¹—the addition of chlorobenzene to acetylene in the presence of aluminum chloride—had given a yellow oil (boiling 210–212° at 30 mm.) having a strong blue fluorescence. The presence of the ethane compound was established by oxidation to 4,4'-dichlorobenzophenone, but the blue fluorescence suggested that impurities of a polycyclic structure were also present.²

Several other preparative methods have now been tried, and it is concluded that 1,1-di-(*p*-chlorophenyl)-ethane is best made as follows: (1) di-(*p*-chlorophenyl)-methylcarbinol,³ prepared from 4,4'-dichlorobenzophenone and methylmagnesium bromide, is (2) dehydrated to 1,1-di-(*p*-chlorophenyl)-ethylene which (3) is hydrogenated to the ethane. Each of these steps proceeds smoothly in good yields: carbinol, 89%; ethylene, 88%; and ethane, 62%.

Pure 1,1-di-(*p*-chlorophenyl)-ethane is a color-

(1) Cook and Chambers, *THIS JOURNAL*, **43**, 334 (1921).

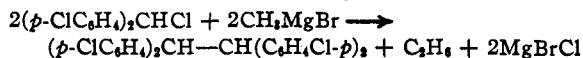
(2) A further reason for suspecting that such impurities were present was the fact that anthracene derivatives have been found along with 1,1-diphenylethane from a closely-related reaction, the Friedel-Crafts reaction of benzene and ethylidene chloride, by Anschütz *et al.*, *Ber.*, **17**, 165 (1884); **18**, 662 (1885); *Ann.*, **235**, 302 (1886).

(3) Bergmann and Bondi, *Ber.*, **64B**, 1455 (1931).

less, crystalline solid melting 54–55°. Neither the solid nor its solutions show any fluorescence in visible or ultraviolet light. Oxidation by chromic acid gives almost quantitative yields of 4,4'-dichlorobenzophenone. The melting point of the ethane is noteworthy in that the next lower homolog, di-(*p*-chlorophenyl)-methane, also melts at 55°.⁴

Direct reduction of the di-(*p*-chlorophenyl)-methylcarbinol at 700–800 lb. pressure and 200–205° in the presence of nickel-on-kieselguhr gave only a 14% yield of the ethane. The condensation of acetaldehyde or acetal with chlorobenzene in the presence of aluminum chloride or sulfuric acid gave 38% of a liquid, fluorescent product comparable to that described by Cook and Chambers.^{1,5} The Friedel-Crafts reaction of ethylidene chloride and chlorobenzene² gave 51% of a liquid product of similar physical properties. Attempts to remove polycyclic impurities from this crude product by selective sulfonation with sulfuric acid or through the formation of addition compounds with picric acid were unsuccessful.

Also tried was the methylation of 4,4'-dichlorobenzohydril chloride with methylmagnesium bromide. This reaction proceeded almost quantitatively through coupling of the 4,4'-dichlorobenzohydril groups to form *sym*-tetra-(*p*-chlorophenyl)-ethane. By analogy with the coupling reactions of benzyl halides with methylmagnesium iodide,⁶ this reaction probably went as



Experimental

1,1-Di-(*p*-chlorophenyl)-ethane.—Since specific directions for the preparation of the di-(*p*-chlorophenyl)-methylcarbinol and the ethylene derivative are not in the literature,³ they are given here. In a one-liter three-neck flask fitted with a stirrer, reflux condenser, and dropping funnel was placed 0.25 mole of methylmagnesium bromide in 115 ml. of ether solution. To this was added during forty-five minutes 63 g. (0.25 mole) of 4,4'-dichlorobenzophenone in 700 ml. of dry thiophene-free benzene. A transient purple color developed during the addition of the ketone, possibly because of the intermediate formation of a bromomagnesium ketyl, (*p*-ClC₆H₄)₂COMgBr.⁷ The reaction mixture was then heated to reflux for one hour, cooled, and hydrolyzed by pouring into a mixture of 27 g. of ammonium chloride, 100 ml. of water and 200 g. of ice. After separating the benzene-ether layer, washing with 100 ml. of 2% sodium carbonate solution, then with 100 ml. of water, and drying with Drierite, the solvent was removed by distillation on the steam-bath. The yield of crude product was 59.3 g., 89% of the theoretical, melting 64–68°. Crystallization from 200 ml. of petroleum ether (90–100°) gave 54.2 g., melting 67–68.5°.

Anal. Calcd. for $C_{14}H_{12}OCl_2$: Cl, 26.58; mol. wt., 267. Found: Cl, 26.62; mol. wt., 266.

The melting point of 167–168° previously reported for this compound is probably the result of a typographical error.³

(4) Montagne, *Rec. trav. chim.*, **25**, 379 (1906).

(5) Bodendorf used the acetaldehyde-chlorobenzene-aluminum chloride reaction for the preparation of 1,1-diphenylethane; *J. prakt. Chem.*, **129**, 337 (1931).

(6) Späth, *Monatsh.*, **34**, 1965 (1913); Fuson, *THIS JOURNAL*, **48**, 2681 (1926).

(7) Gomberg and Bachmann, *ibid.*, **49**, 236 (1927).